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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/479,038	06/07/1995	William N. Drohan	1327.0440006	7774

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EXAMINER	
MARSCHEL, ARDIN H	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/479,038	DROHAN ET AL.	
	Examiner	Art Unit	
	Ardin Marschel	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2000*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,13,17-20,24-32 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,13,17-20,24-32 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 6/7/95 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date (41 sheets)
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. 8/28/00 and 6/29/04
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Attachment for PTO-948*.

DETAILED ACTION

Applicants' arguments, filed 8/4/00, have been fully considered and they are deemed to be persuasive to overcome all previous rejections of record in a timely fashion. Therefore, applicants had fully satisfied their response duty as of 8/4/00. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Therefore, correspondingly, the finality of the Office action, mailed 11/5/99, is hereby withdrawn. This withdrawl of finality also is deemed to make the Notice of Appeal, filed 5/5/00, moot.

Regrettably, a very significant delay has occurred in further consideration of this application. Unfortunately, albeit after said delay, a review of the instant application has revealed important issues that are summarized below.

CHANGE OF INVENTORSHIP

The granting of the Petitions for waiver of 37 CFR § 1.48(a)(3) under 37 CFR § 1.183 and 37 CFR § 1.48(a) to correct inventorship, mailed 12/1/03, is acknowledged. This has resulted in the addition of Hernan Nunez, Gene Liau, Wilson H. Burgess, and Thomas Maciag being listed as inventors on the instant application.

The following rejections and/or objections are newly applied. They constitute the complete set presently being applied to the instant application.

INFORMATION DISCLOSURE STATEMENTS

Several IDSs with PTO Forms 1449 have been filed in the previous few months. Executed copies of these 1449s are enclosed. Several citations have been lined

through thereon due to lacking publication dates, however, they have been considered. Twelve Japanese documents and one German document were lined through on the IDS, filed 11/20/02, due to not being considered due to being in a foreign language. It is acknowledged that the following related U.S. Patent applications have also been considered: 07/618,419; 07/798,919; 08/031,164; 08/328,552; 08/351,006; 08/479,034; 08/485,882; 08/485,883; 08/485,898; 08/486,048; 08/483,088; 08/474,086; 08/474,084; 08/474,078; 10/465,860; 10/465,854; and 10/465,853.

DRAWING INFORMALITIES

Applicant is hereby notified that the required timing for the correction of drawings has changed. See the last 6 lines on the sheet which is attached entitled "Attachment for PTO-948 (Rev. 03/01 or earlier)". It is noted that a PTO Form 948 is mailed herewith. Due to the above notification Applicants are required to submit drawing corrections within the time period set for responding to this Office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office action.

TITLE

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The presently pending claims are all drawn to supplement delivery systems which are reasonably deemed products of compositions, whereas, in contrast, the present title is directed to method of production and use.

NEW MATTER

Claims 12, 13, 17-20, 24-32, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

NEW MATTER has been added to the claims via the phrase "said sustained period is greater than the period obtained according to simple diffusion kinetics" as in the last 2 lines of independent claims 12, 34, and 36. The NEW MATTER which has been added is the broadening of this practice compared to the closest, and only found, citation as filed directed to this practice. The citation regarding "simple diffusion kinetics" is found in the paragraph on page 72, lines 12-19. Herein the delivery of TGF-β2 is stated as being released via a requirement of the "dissolution of the fibrin clot" and that the "mechanism of delivery from the TGF- β2 supplemented tissue sealant composition is readily distinguished from simple diffusion kinetics". In this citation several distinctions exist compared to the claim amending noted above as containing NEW MATTER. Firstly, only the growth factor, TGF- β2, is cited as being delivered with the fibrin clot dissolution requirement and is readily distinguished from simple diffusion kinetics. This contrasts with a lengthy list of supplements in the instant claims inclusive of a cytotoxin, anesthetic, steroid, antibiotic, lipid, vitamin, etc. to name only a few. These other supplements vary greatly compared to TGF- β2 in molecular properties, such as size, shape, reactivity to surrounding materials, etc. and so would not even be

reasonably exemplified by only TGF-β2 practice. Secondly, this citation fails to give written basis for the "greater than the period" limitation that is present in the last two lines of the instant independent claims. The delivery mechanism being distinguished from simple diffusion kinetics lacks any comparative time period disclosure in said page 72 description. Thirdly, the page 72 citation requires fibrin clot dissolution as the controlling mechanism for TGF-β2 delivery compared to simple diffusion kinetics which is not present as an accompanying limitation in the last two lines of the instant independent claims. Thus, the last two lines of the instantly pending independent claims clearly contain NEW MATTER. Claim which depend from the instant independent claims also contain this NEW MATTER due to their dependencies.

Also, NEW MATTER has been added to the instant independent claims 12 and 34 via the phrase "said effective amount of said supplement is greater than the amount which is soluble in said fibrin matrix"; as in claim 12, lines 14-15; and claim 34, lines 16-17. The NEW MATTER which has been added is the broadening of this practice compared to the closest, and only found, citation as filed directed to this practice. The only citation regarding the supplement amount compared to an amount which is soluble in a fibrin matrix is in the specification on pages 107-109 in Example 21. Firstly, only taxol or paclitaxel is described in this Example, especially noting on page 109, lines 10-12, wherein a specific explanation of its insolubility being dependent on its molecular weight compared to ethanol thus leaving the taxol or paclitaxel to precipitate in solid form within the matrix. This citation is not directed to any supplement as included in the lengthy list of such supplements in the presently pending claims as also noted in the

above NEW MATTER explanation. Thus, this broadening of the instant claims is NEW MATTER compared to the disclosure as filed. Secondly, the fibrin matrix content of taxol is based on its "insolubility" and not on what is soluble therein as now claimed. Thus, claims 12 and 34 and claims which depend directly or indirectly therefrom contain this NEW MATTER.

LACK OF SCOPE OF ENABLEMENT

Claims 12, 13, 17-20, 24-32, and 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the practice of forming a fibrin matrix utilizing fibrinogen in the presence of thrombin, Ca^{++}, and water, does not reasonably provide enablement for the practice of forming a fibrin matrix from a derivative or metabolite of thrombin in the presence of thrombin, Ca^{++}, and water. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those

in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case are discussed below.

No guidance has been found as filed as to what derivation or metabolism action on fibrinogen will predictably result in a derivative or metabolite which yet forms a fibrin matrix in the presence of thrombin, Ca^{++}, and water. Since fibrinogen is a reasonably complex protein its conversion to a fibrin matrix will require complex molecular interactions which are not set forth as explained as filed which may then be utilized to predict what derivation or metabolism may occur without defeating fibrin matrix formation as a capability of such a derivative or metabolite. Prior art knowledge of what derivation or metabolism still leaves a material which can form a fibrin matrix is also not seen as being well known. Therefore, the practice of making a derivative or metabolite of fibrinogen which can form a fibrin matrix in the presence of thrombin, Ca^{++}, and water is unpredictable and therefore requires undue experimentation to make and therefore is not enabled.

VAGUENESS AND INDEFINITENESS

Claims 12, 13, 17-20, 24-32, and 34-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12, line 9, cites "said derivative or metabolite thereof" which apparently is meant to refer to a fibrinogen derivative or metabolite thereof. Such a derivative or metabolite was deleted in a previous amendment in lines 6-7 of claim 12. Therefore, said phase in line 9 lacks clear antecedent basis as to what it refers to. Similarly, claim 36, line 10, also contains the above phrase which lacks clear antecedent basis due to previous claim amending deletion of an antecedent phrase. Clarification via clearer claim wording is requested. Claims which depend directly or indirectly from claim 12 also contain this unclarity due to their dependence.

All of the presently pending claims either directly or via dependence cite the phrase "derivative or metabolite thereof" apparently referring to a derivative or metabolite of fibrinogen. Consideration of the instant disclosure as filed has failed to reveal a definition of the metes and bounds of such a derivative or metabolite and none is known in the art. Therefore, without some type of limitation(s) as to the metes and bounds of such a derivative or metabolite these limitations cause the instant claims to be vague and indefinite. Clarification via clearer claim wording is requested. It is noted that claim 12, lines 9-11, indicates that, optionally, such a derivative or metabolite will form a fibrin matrix in the presence of thrombin, Ca^{++}, and water. The instant disclosure as filed does not describe what metes and bounds define how much derivation or metabolism action still leaves a resulting derivative or metabolite of fibrinogen still able to form such a matrix in the presence of the three materials, thrombin etc. Therefore, the requirement for forming a fibrin matrix in the presence of the three materials, thrombin, etc. also fails to give a clear and concise definition of the metes and bounds of such a derivative or metabolite.

PRIOR ART

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 18, 25, 29-32, and 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marx [(P/N 5,607,694); already of record]; taken in view of Popescu et al. (P/N 4,708,861).

It is firstly noted that the presence of NEW MATTER in the claims prevents granting of priority for any of the instant claims to parent applications. Thus, at best the instant claims are granted priority only to the instant application filing date of June 7,

1995. The above two references have effective filing dates and/or issue dates prior to June 7, 1995.

Marx describes the components of the instantly claimed invention. The abstract of Marx describes its invention as being a biologically compatible (biocompatible as instantly claimed) sealant composition comprising fibrin glue and liposomes. Said liposomes contain bioactive substances (supplements as instantly claimed) which may be released to promote healing etc. The liposome content of supplements are in effective amounts as cited in column 10, lines 3-45, as also instantly a claim limitation. A wide variety of supplements are listed in column 11, line 19, through column 12, line 35, inclusive of growth factors, antibiotics, proteins (polypeptides as instantly claimed), and cytokines to note a few of a lengthy list in Marx corresponding to supplements as instantly claimed. The fibrinogen in the fibrin glue of the invention of Marx is cited as forming a fibrin clot (reasonably a fibrin matrix as instantly claimed) in column 8, lines 6-65, inclusive of the presence of thrombin, Ca(II) which is Ca++ as instantly claimed, and suggesting the presence of water, or an aqueous environment, due to the usage of the invention on wounds which clearly contain water or are an aqueous environment with water containing blood. Factor XIII may also be present with fibrinogen as cited in column 2, lines 5-11, as also required in instant claim 31. A protein being fibrinogen may also be recombinantly produced as cited in Marx in column 2, lines 33-47, as required in instant claim 37. These materials are present in the fibrin glue prior to formation of the fibrin matrix in-situ thus including embodiments as required for instant claim 17. The delivery of supplements for a sustained period as in instant claim 36,

lines 13-14, is described in column 5, lines 18-25, where a controlled fashion is described for liposome content release. This is more detailed in column 3, lines 35-58, wherein sustained release of the liposome content is discussed and suggested/motivated as being further explained in U.S. Patent 4,708,861.

U.S. Patent 4,708,861 by Popescu et al. further details liposome compositions for such sustained release as summarized in the abstract and in column 3, lines 39-63. In column 4, lines 2-20, Popescu et al. describes bioactive agent release that is a slow release due to entrapment in liposomes. Such entrapment is reasonably interpreted as slowing release of bioactive agents or supplements via physical barrier entrapment which limits release of supplements to a rate that would be slower than diffusion of non-entrapped materials would permit. It is acknowledged that a comparison of release to simple diffusion kinetics as instantly claimed in the last two lines of instant claim 36 is not specifically cited in the reference, however, physical entrapment is reasonably interpreted to be slower than simple diffusion kinetics. Therefore, it is reasonable to view such release as resulting in a sustained period of release which is greater than what would be obtained from simple diffusion kinetics as instantly claimed in the last two lines of instant claim 36.

Thus, it would be obvious to someone of ordinary skill in the art at the time of the instant invention to practice the liposome/fibrin glue supplement delivery system of Marx wherein sustained release of supplement(s) is over a greater sustained period than obtainable from simple diffusion kinetics due to the entrapment descriptions in Popescu et al. thus resulting in the practice of the instant invention. Since it is reasonable that

the above combination of references suggests and motivates the instant invention but does not specifically contain a description of a sustained period of release compared to simple diffusion kinetics, the burden to distinguish the instant invention from the above summarized combination of references is shifted to applicants as stated in the following paragraph. Applicants are reminded that the U.S. Patent & Trademark Office does not have laboratory facilities to test for chemical characteristics of prior art materials as cited in the instant claims in order to determine the presence or absence of such characteristics in prior art cited materials. It is noted that antibiotics are included as supplements cited in Marx and reasonably carry with them the property of increasing longevity of a fibrin matrix as described in instant claims 18 and 35. Therefore, the burden is also shifted to applicants to distinguish the instant invention from the above summarized combination of references which reasonably disclose antibiotics which have the property cited in instant claims 18 and 35.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claims 12, 13, 18, 30-32, 34, and 36 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Schlag et al. [Clinical Orthopaedic and Related Res. Vol. 227:269 (1988); already of record].

Schlag et al. discloses fibrin sealants in the abstract and title. In the last paragraph in the righthand column of page 269, the reference discloses a fibrin sealant which contains fibrinogen, enhanced Factor XIII content and aprotinin as an inhibitor of fibrinolysis (which is expected to increase fibrin matrix longevity as in instant claim 18). On page 270, lefthand column, first paragraph, this sealant cited as being available as a freeze dried powder along with a solution of thrombin, Calcium chloride [well known salt containing Ca^{++}]. In instant claim 36 at least two components are cited as fibrinogen and a protease inhibitor (aprotinin) with properties such as ability to form a fibrin clot in the presence of thrombin etc., a supplement deliverable for a sustained period which is greater than the period obtained due to simple diffusion kinetics. The formation of a fibrin clot from fibrinogen under the claimed conditions is fully expected as fibrinogen is well known to have that capability. The formation of a clot would be expected to entrap at least some of the aprotinin (a supplement as instantly claimed) in order to slow its release over a sustained period as well as releasing it only upon fibrin matrix or clot dissolution which is clearly for a sustained period greater than obtained via simple diffusion kinetics. It is additionally noted that a clot such as a fibrin matrix formed from fibrinogen etc. is reasonably expected to have little solubility for any chemical including aprotinin and thus instant claims 12 and 34 are included hereinunder which additionally has a solubility limitation in each claim. Thus, the above noted disclosure in Schlag et al. inherently cites the claimed invention, or, alternatively, would be reasonably expected to contain these components with the instantly claimed characteristics. Applicants are reminded that the U.S. Patent & Trademark Office does not have

laboratory facilities to test for chemical characteristics of prior art materials as cited in the instant claims in order to determine the presence or absence of such characteristics in prior art cited materials. In this case the burden is shifted to applicants to distinguish the description in the reference from the claimed instant invention. See the following paragraph.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

INFORMALITIES

The disclosure is objected to because of the following informalities:

The Brief Description of the Figures section starting on page 25 of the instant specification contains several inconsistencies as compared to the actual Figures summarized as follows:

1) The Figure 1 Brief Des. cites HBGF-1β whereas, in contrast, Figure 1 cites ECGF. Also the heparin amounts in the Figure panels is given as “u/ml” whereas, in contrast, the Brief Des. cites “U/ml”. It is noted that several unit definitions in the art differentiate between capitalized Units vs. small letter units as to the quantities meant thereby.

2) The Figure 2 Brief Des. cites HBGF-1β or HBGF-1, whereas, in contrast, ECGF is cited in Figure 2. The Figure 2 Brief Des. cites concentrations of thrombin and heparin in "U/ml" whereas Figure 2 cites amounts of these materials in "U" values which is not generally interpreted as a concentration. Within the Figure 2 Brief Des. the growth factor in inconsistently cited as HBGF-1β vs. HBGF-1.

3) HBGF-1 is cited in other Figure Brief Descriptions which confusingly may or may not be different from HBGF-1β.

Appropriate correction is required.

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the Central PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center number is (703) 872-9306.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (571) 272-0718. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

June 29, 2004

Ardin H. Marschel 7/1/04

APPROVED
MARY C. LEE
DIRECTOR, GROUP 1600